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EXAMINER	
NEGIN, RUSSELL SCOTT	
ART UNIT	PAPER NUMBER
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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/523,353	YANG, QING	
	Examiner	Art Unit	
	RUSSELL S. NEGIN	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *14 April 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,4-25,30-38 and 41-52* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,4-25,30,31,33-38,41-49,51 and 52* is/are rejected.

7)☒ Claim(s) *32 and 50* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *4/14/08*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Comments

Applicants' amendments and request for reconsideration in the communication filed on 14 April 2008 are acknowledged and the amendments are entered.

Claims 1, 4-25, 30-38, and 41-52 are pending and examined in the instant Office action.

Information Disclosure Statement

The information disclosure statement of 14 April 2008 is considered.

Priority

Acknowledgment is made of applicant's claim for foreign priority based on an application filed in Australia on 30 April 2004. It is noted, however, that applicant has not filed a certified copy of the 2004902360 application as required by 35 U.S.C. 119(b).

Claim Objections

Claims 32 and 50 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims. (It is noted that claim 32 depends from claim 50.) Claim 50 is free of the prior art because the prior art does teach or suggest the tissue transport function is in the specific Gaussian function taught

in instant claim 50 with the specific restrictions taught on the variable A2 (i.e. the equations governing the error functions as recited in the penultimate line of instant claim 50).

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

The following rejection is necessitated by applicant's amendment for instant claims 51-52 and is newly applied for claims 36-37:

Claims 36-37 and 51-52 are rejected under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter.

Claims 36-37 recite a "computer program means for..." wherein a computer program, per se, is not statutory subject matter.

Since claims 51 and 52 recite "computer readable media," and the specification is silent on what constitutes such computer readable media, the instant claims are interpreted broadly to encompass carrier waves, which, per se, are not statutory.

Claim Rejections - 35 USC § 112

The rejections of claims 14-25 and 34-35 under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the

subject matter which applicant regards as the invention are withdrawn in view of amendments filed by applicants to the instant claims filed on 14 April 2008.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

ENABLEMENT

Claims 7-11, 22-25, 44-47, and 49 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention. While the claims explicitly recite the intended equations, the claims and specification do not teach how to initially calculate σ_1 and α_1. Without a clear representation and calculation of the variables, it is not understood how to execute the steps of the equations recited within the instant claims.

1. The claimed subject matter is broad such that the variables σ_1 and α_1 are ***related*** to mean transit time and dispersion (i.e. see last two lines of instant claim 7). However, there is no explicit direction on how to initially calculate the variables, σ_1 and α_1 nor any teaching for what the "relationship" is intended to be.

2. Equation 13 on page 18 describes how the optimized variables are USED to compute specific properties regarding transit times and dispersion times. Furthermore,

equation 8b on page 17 of the specification gives a starting point in terms of peak height, but this relation is for σ_2 and NOT σ_1. The specification is silent on how to calculate σ_1 and α_1 in order to determine such transit and dispersion times.

3. In the prior art of Fogler [Elements of Chemical Reaction Engineering, 2nd Edition, 1992, section 13.4, pages 729-737], the equations throughout 13.4 use many variables regarding time (i.e. residence time, reaction time, dimensionless times). As it is already unclear as to what the values of σ_1 and α_1 are (see discussion above), it is additionally unclear as to what quantities they represent. Consequently, it is further unclear as to how to "map" the variable conventions of the instantly rejected claims with those of Fogler. Since it is unknown as to what σ_1 and α_1 represent, one of skill in the art is left guessing as to which variable of the instantly rejected claims map to which corresponding variable in Fogler. Such guessing amounts to undue experimentation.

4. In view of the above, it is the Examiner's position that with the insufficient guidance and working exampled and in view of unpredictability and the state of the art one skilled in the art could not make and/or use the invention with the claimed breadth without an undue experimentation.

INDEFINITENESS

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 10-11, 17-21, 34-35, and 47 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 10 recites an IRF $R_e(t)$ in the second line of the claim.

Claim 17 recites a simulated tissue IRF $R_s(t)$ in the second line of the claim.

Claim 34 also recites a simulated tissue IRF $R_s(t)$ in the second line of the claim.

While claim 47 recites an initial impulse residue function $R_o(t)$ in step (i) of the claim, step (iv) of the same claim recites the tissue IRF Re(t) from a different deconvolution.

Given these different used of the term "IRF," it is not clear as to whether an "IRF" is an impulse residue function, or a different function altogether.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following rejection is reiterated from the previous Office action and is necessitated by amendment for claims 51-52:

Claims 1, 4-6, 36-38, 41-43, and 51-52 are rejected under 35 U.S.C. 102(e) as being anticipated by Ostergaard [US Patent 7,069,068; issued 27 June 2006; entered national stage 15 November 2001].

Claim 1 is drawn to a method of deriving blood perfusion indices for a region of interest (ROI) of a subject.

--administering a contrast agent to the subject during a dynamic imaging scan;

--converting signal intensity data from raw images of the scan into contrast agent concentration data;

--deriving parameters from the contrast agent concentration data using at least one transport function that accounts for delay and dispersion of the contrast agent, wherein the at least one transport function includes an arterial transport function $h_a(t)$ represented by a first model through a vessel leading to the ROI; and

--calculating the blood perfusion indices from the derived parameters.

Claim 4 is further limiting wherein the at least one transport function further comprises a tissue transport function $h_s(t)$ represented by a second model through the ROI.

The invention of Ostergaard describes a method for determining hemodynamic indices by the use of tomographic data. The abstract of Ostergaard explains:

> Haemodynamic indices of an organ or a part of tissue are determined from a time series of tomographic data obtained by means of Magnetic Resonance Imaging. Maps of indices are produced. Maps of indices are produced, being significant of the dynamics of the capillary tissue flow acquired during rapid bolus injection of a tracer that stays mainly intravascular.

Consequently, blood perfusion indices are identified in regions of interest of the body (i.e. preamble of instant claim 1).

The MRI imaging protocol described in column 16, line 62 to column 17, line 12 of Ostergaard describes imaging of a contrasting agent during dynamic image scanning (i.e. first step of instant claim 1).

Equation 15 of column 17 in Ostergaard converts signal intensity data from raw images to concentration data (i.e. second step of instant claim 1).

Equations 11 and 12 in column 15 of Ostergaard et al. also show how to derive parameters (i.e. the matrices in Equation 12) and calculate blood perfusion indices (i.e. CBF in Equation 12 of Ostergaard) using a transport function (i.e. Equation 11 of Ostergaard). The numerical process of the solving of these two equations is stated in column 17, lines 50-58 of Ostergaard (i.e. third and fourth steps of claim 1).

Example 3 starting in column 27, line 5 of Ostergaard exemplifies modeling cerebral blood flow with the required arterial transport function listed in equations 21-22 in column 29 of Ostergaard.

Example 5 starting in column 42, line 25 of Ostergaard exemplifies modeling renal plasma flow with the required tissue transport function listed in equations 27-29 in column 45 of Ostergaard.

Claim 5 is further limiting comprising the step of selecting an arterial input function in the vessel leading to the ROI by searching pixels taken of the contrast agent concentration data.

Claim 6 is further limiting comprising the step of measuring the contrast agent concentration remaining in the ROI.

Column 27, lines 45-50 of Ostergaard details the use of the AIF and pixels taken from the contrasting agent data.

Equation 19 in column 28 details the concentration of agent as a function of time.

Claim 36 is further limiting wherein there is a computer program means for deriving blood perfusion indices for a region of interest.

Claim 37 is further limiting wherein the computer program means is further directed to retrieving raw image data from the dynamic imaging scan after a contrast agent is administered to the subject.

Claim 23 of Ostergaard recites the computer means for performing the aforementioned invention of Ostergaard.

Claim 38 is drawn to a system for performing the method of instant claim 1.

Column 5, lines 22-56 of Ostergaard detail the system for performing the method of instant claim 1.

Claim 41 is further limiting comprising a second model to represent a tissue transport function through the ROI.

Example 3 starting in column 27, line 5 of Ostergaard exemplifies modeling cerebral blood flow with the required arterial transport function listed in equations 21-22 in column 29 of Ostergaard.

Example 5 starting in column 42, line 25 of Ostergaard exemplifies modeling renal plasma flow (i.e. a second model) with the required tissue transport function listed in equations 27-29 in column 45 of Ostergaard.

Claim 42 is further limiting comprising the step of selecting an arterial input function in the vessel leading to the ROI by searching pixels taken of the contrast agent concentration data.

Claim 43 is further limiting comprising the step of measuring the contrast agent concentration remaining in the ROI.

Column 27, lines 45-50 of Ostergaard details the use of the AIF and pixels taken from the contrasting agent data.

Equation 19 in column 28 details the concentration of agent as a function of time.

Claim 51 is further limiting comprising a computer readable medium storing a program for deriving blood perfusion indices for a region of interest of a subject by directing a processor to carry out the method steps of claim 1 apart from the step of administering a contrast agent to the subject during a dynamic imaging scan.

Claim 52 is further limiting comprising a computer readable medium storing a program according to claim 36, the program further directing the processor to retrieve

raw image data from the dynamic imaging scan of the subject after a contrast agent is administered to the subject.

As explained above, column 16, line 62 to column 17, line 12 of Ostergaard describes imaging of a contrasting agent during dynamic image scanning. Claims 23 and 25 of Ostergaard describes the use of a computer to execute the process.

Response to Arguments:

Applicant's arguments filed 14 April 2008 have been fully considered but they are not persuasive.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., a non-linear- i.e. not an SVD deconvolution method, see pages 17-19 of Remarks) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993). For example, applicant states on page 18 of the Remarks, "Thus, the SVD deconvolution method described in Ostergaard's patent ***is unable to distinguish arterial delay and dispersion*** from prolonged tissue MTT and hence impairs its clinical application." However, the instant claim in question does not have this highlighted limitation; instead instant claim 1 recites, "...transport function that ***accounts for delay and dispersion*** of the contrast agent..." Consequently, there is no *distinguishing between* delay and dispersion recited in the instantly rejected claims.

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e., features of interest in Figure 3 of the instant application; see page 18 of the Remarks) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

Applicant next argues on page 19-20 of the Remarks that equations 21-22 of column 29 of Ostergaard used to anticipate instant claim 1 are arterial INPUT functions and NOT arterial transport functions. Assuming this argument is accurate, the rejection of claim 1 also cites transport functions listed in equations 27-29 in column 45 of Ostergaard. However, it is not understood from the claimed language and the specification as to how an input function differs from a transport function as "transport" necessarily includes "input."

Claim Rejections - 35 USC § 103

The rejections of claims 7-9 under 35 U.S.C. 103(a) as being unpatentable over Ostergaard in view of Fogler [Elements of Chemical Reaction Engineering, 2nd Ed, 1992, chapter 13, section 13.4, pages 729-737] are withdrawn due to reconsideration and the enablement rejection recited above.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The following rejection is NEWLY applied:

Claims 12-16 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ostergaard as applied to claims 1, 4-6, 26-29, 36-38, 41-43, and 51-52 above, and further in view of Fogler [Elements of Chemical Reaction Engineering, 2nd Ed, 1992, chapter 13, section 13.4, pages 729-737].

Claims 1-6 recite a method of deriving blood perfusion indices for a region of interest, as set forth above.

Claim 14 is further limiting comprising the step of representing h(t) using a gamma variate function using the equations listed on page 5 of the instant claims.

Claim 15 is a species of the equations in instant claim 7 with some of the parameters set to zero.

Claim 16 is further limiting by showing the relevant convolution integral for determining the estimate of the arterial input function at the entry of the ROI.

Claims 12 and 13 are further limiting comprising calculating a rise time and a mean transit time.

Ostergaard teaches determination of blood perfusion indices for an injection of a bolus into a blood stream, as set forth above. Ostergaard further teaches a convolution integral, in Equation 19 in column 29 similar to that of instant claim 16.

However, Ostergaard does not explicitly quantify the gamma variate function as required by instant claims 14 and 15.

Fogler teaches a generic approach to teaching residence time distributions in reactors and step tracer analysis in Chapter 13. Specifically, equation 13-42 (page 731) and equation 13-50 (page 734) taken in combination teach the limitations of the equations in instant claims 14-15. Figures throughout section 13.4 of Fogler (i.e. Figures 13-7 and 13-8) teach a rise time and a mean transit time.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the method of determining perfusion indices of Ostergaard by use of the residence time distributions of Fogler because it is obvious to apply a known technique to a known method to yield a predictable result. In this instance, it would have been obvious to apply the known technique of residence time distribution modeling of Fogler to the blood perfusion modeling of Ostergaard where the result would have been additional modeling of blood in a physiological system. There is a reasonable expectation of success because both methods (Ostergaard and Fogler) are drawn to step tracer analyses (i.e. injecting a bolus of reactant into a flowing reactor or body and modeling its distribution over time), and Fogler gives more specific equations by which the blood perfusion studies of chemical injections could be advanced.

Response to Arguments:

In response to applicant's argument that the examiner's conclusion of obviousness is based upon improper hindsight reasoning, it must be recognized that any judgment on obviousness is in a sense necessarily a reconstruction based upon

hindsight reasoning. But so long as it takes into account only knowledge which was within the level of ordinary skill at the time the claimed invention was made, and does not include knowledge gleaned only from the applicant's disclosure, such a reconstruction is proper. See *In re McLaughlin*, 443 F.2d 1392, 170 USPQ 209 (CCPA 1971).

In response to applicant's argument that the references fail to show certain features of applicant's invention, it is noted that the features upon which applicant relies (i.e. known vs. unknown structures) are not recited in the rejected claim(s). Although the claims are interpreted in light of the specification, limitations from the specification are not read into the claims. See *In re Van Geuns*, 988 F.2d 1181, 26 USPQ2d 1057 (Fed. Cir. 1993).

The following rejection is NEWLY applied:

Claims 30-31 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Ostergaard as applied to claims 1, 4-6, 26-29, 36-38, 41-43, and 51-52 above, and further in view of Meaney et al. [US Patent 5,924,987; issued 20 July 1999; filed 6 October 1997; on IDS] in view of Wu et al. [US PGPUB 2007/0112264 A1; issued 17 May 2007].

Claim 30 is further limiting wherein the vessel is an artery, the method further comprising determining a venous input function from a draining vein to estimate an arterial input function where a selected artery has partial voluming. Claim 31 is further limiting comprising determining the profile of the venous input function from the draining

vein. Claim 48 is further limiting comprising the step of scaling the arterial input function to the venous input function.

Ostergaard teaches determination of blood perfusion indices for an injection of a bolus into a blood stream, as set forth above.

However, Ostergaard does not teach partial voluming or use of a venous input function.

The invention of Meaney et al. is drawn to a method and apparatus for magnetic resonance arteriography using contrast agents. The abstract of Meaney et al. goes into detail of how partial voluming is used to scan a patient's body in addition to the relation between intensities from the contrast agents in the veins and arteries of the patient.

However, Ostergaard and Meaney et al. do not teach explicit use of a venous input function.

The application of Wu et al. teaches calculation of tissue blood flow.

Specifically, the abstract and cover figure of Wu et al. teach methods for computing perfusion parameters. Paragraph 44 of Wu et al. teaches that one of the parameters may be a venous input function.

It would have been obvious to someone of ordinary skill in the art at the time of the instant invention to modify the method of determining perfusion indices of Ostergaard by use of the partial voluming in Meaney et al. wherein the motivation would have been that partial voluming of a patient allows for a greater region of the patients' circulatory system to be investigated [see, for example, column 6, lines 45-55]. It would have been further obvious to modify the imaging and analysis techniques of Ostergaard

and Meaney et al. by use of the venous input function of Wu et al. because it is obvious to combine known elements in the prior art to yield a predictable result. In this instance, combining the imaging and analysis studies for arterial properties with the venous properties of Wu et al. would have yielded an alternate analysis of the venous rather than arterial data. There would have been a reasonable expectation of success in combining Ostergaard, Meaney et al., and Wu et al. because as arteries and veins are part of the circulatory system, they are analogous organs to which blood flow imaging and analysis are applicable.

Conclusion

No claim is allowed.

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the central PTO Fax Center. The faxing of such pages must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993)(See 37 CFR § 1.6(d)). The Central PTO Fax Center Number is (571) 273-8300.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Russell Negin, Ph.D., whose telephone number is (571) 272-1083. The examiner can normally be reached on Monday-Friday from 7am to 4pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Marjorie Moran, Supervisory Patent Examiner, can be reached at (571) 272-0720.

Information regarding the status of the application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information on the PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/RSN/
Russell S. Negin, Ph.D.
9 August 2008

/Marjorie Moran/
Supervisory Patent Examiner, Art Unit 1631